

RESEARCH PROTOCOL

MOSART-study

Neurotoxic adverse effects of morphine and oxycodone in continuous subcutaneous infusion for treatment of pain in terminal patients with diminished renal function: a Randomized Controlled Trial.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
ADR	European Agreement concerning the International Carriage of Dangerous Goods by Road; in French: Accord européen relatif au transport international des marchandises Dangereuses par Route
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology collaboration
COV	Close-Out Visit
CRF	Case Report Form
CSCI	Continuous Subcutaneous Infusion
CTCM	Clinical Trial Center Maastricht
CV	Curriculum Vitae
DOS	Delirium Observation Screening
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4 th edition, Text Revision
DSMB	Data Safety Monitoring Board
eGFR	Estimated Glomerular Filtration Rate
EORTC	European Organization for Research and Treatment of Cancer-Quality of Life
QLQ-C30	Questionnaire-Core 36
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
ICH-GCP	ICH Good Clinical Practice
IKNL	Netherlands Comprehensive Cancer Organisation; in Dutch: Integraal Kankercentrum Nederland
IMP	Investigational Medicinal Product
IMPd	Investigational Medicinal Product Dossier

IMV	Interim Monitoring Visit
KNMG	Royal Dutch Medical Association; in Dutch: Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst
KNMP	Royal Dutch Pharmacists Association; in Dutch: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie
M3G/M6G	Morphine-3-Glucuronide / Morphine-6-Glucuronide
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
MUMC	Maastricht University Medical Centre; in Dutch: Maastricht Universitair Medisch Centrum
NMDA	N-methyl-D-aspartate
NRS	(0-10 Verbal) Numeric Rating Scale
NTAE	Neurotoxic Adverse Effects
OIH	Opioid Induced Hyperalgesia
OR	Odds Ratio
PG	PsychoGeriatric
QoDD	Quality of Dying and Death
REPOS	Rotterdam Elderly Pain Observation Scale
RCT	Randomized Controlled Trial
ROO	Rapid-Onset Opioid
(S)AE	(Serious) Adverse Event
SIV	Site Initiation Visit
SPC	Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
WBP	Personal Data Protection Act; in Dutch: Wet Bescherming Persoonsgegevens
WGBO	Dutch Medical Treatment Act; in Dutch: Wet op de Geneeskundige Behandelingsovereenkomst
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: The prevalence of significant pain at the end of life is high. Continuous subcutaneous infusion (CSCI) of opioids is the cornerstone in treatment of pain in this last phase of life. Although morphine is the most frequent used opioid in this respect, its main metabolites – morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) – start to accumulate when renal function decreases. The accumulation of M3G is associated with neurotoxic adverse effects like delirium, allodynia and hyperalgesia. The central effects of circulating metabolites of oxycodone, on the other hand, are negligible. On theoretical considerations CSCI of oxycodone for the treatment of pain in dying patients with a diminished renal function should therefore result in a reduced occurrence of the neurotoxic adverse effects delirium and allodynia/hyperalgesia in comparison to morphine. However, studies of sufficient quality investigating the clinical effect of this hypothesis are lacking at the moment.

Objective: The primary objective of this study is to compare the prevalence of delirium between oxycodone and morphine, administered by CSCI, for the treatment of pain in dying patients with a diminished renal function. The secondary objective is to compare the prevalence of allodynia/hyperalgesia between these two opioids.

Study design: A randomized, controlled, observer blinded, multicentre, superiority trial with to parallel groups with an 1:1-allocation-ratio.

Study population: Residents of hospices and somatic or psychogeriatric (PG) wards of nursing homes, 18 years or older, who are eligible for start of CSCI of an opioid for the treatment of pain in the terminal phase of life. 117 patients per group are needed.

Intervention: One group receives CSCI of oxycodone and the other group CSCI of morphine.

Main study parameters/endpoints: The main study parameter is the difference in occurrence of delirium at any time between start of CSCI of morphine or oxycodone and death. The secondary parameter is the difference in occurrence of allodynia/hyperalgesia. The Delirium Observation Screening (DOS)-scale is used for screening for presence for delirium. The clinical diagnosis of delirium is confirmed or rejected in accordance with the DSM-IV-TR criteria. Brushing with a piece of cotton wool on the skin and pin-prick testing is performed to assess for presence of allodynia/hyperalgesia. Items of the Rotterdam Elderly Pain Observation Scale (REPOS) are used to determine presence of pain in subjects who are verbally inadequate responsive. All parameters are assessed three times a week until death of the participant.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Since the investigated products are registered products to be used in

regular care for the registered indication and route of administration, and not in combination with other products, participants are not exposed to any additional medication-related risks. A one-time blood collection by venipuncture at the first visit is performed to assess renal function. The risk of venepuncture-related complications is considered low. The burden associated with assessment for delirium and allodynia/hyperalgesia three times a week is considered low. It is essential to not exclude an incapacitated (psychogeriatric) population in this study to best represent usual care, since the major part of dying patients experiences a decline in cognitive functions and are not able to respond adequately anymore. Special attention will be paid to signs of objection or resistance to any of the study procedures by incapacitated subjects.

1. INTRODUCTION AND RATIONALE

The prevalence of significant pain at the end of life has been estimated to be around 50% in the last 1-2 months prior to death and 30-75% in the last days of life (1-4). Continuous subcutaneous infusion (CSCI) of opioids has become the cornerstone in treatment of pain in dying patients (5, 6). Both continuous subcutaneous administration by a syringe driver and scheduled intermittent subcutaneous injections are equal in analgesic effectiveness and side effects (7). Morphine is the most frequent used opioid in this respect (8, 9).

Morphine, metabolites and renal impairment

The two major metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). These two metabolites are excreted renally (10). Multiple pharmacological studies have shown that accumulation of M3G and M6G already occurs in mild renal impairment (11-13). For this reason, the Dutch guideline for the diagnosis and treatment of pain in cancer patients advises to better refrain from prescribing morphine in patients with an estimated glomerular filtration rate (eGFR) of <50 ml/min (14). This threshold of <50ml/min means that, even in healthy subjects, accumulation of active morphine metabolites starts to be relevant at the age of 70 due to an age-dependent decline of renal function (15). Physiological changes in terminally ill patients contribute to an almost inevitable relevance of this phenomenon in the terminal phase of life: a recent study of the pharmacokinetics of morphine, M3G and M6G in terminal ill patients has shown accumulation of these metabolites due to a decline in renal function (12).

M6G contributes to an important extent to the analgesic properties of morphine (16-18). M3G, on the contrary, is considered to play no role or even an antagonistic role in analgesia and is associated with neurotoxic adverse effects like hyperalgesia, allodynia, myoclonus, insults and delirium in animal studies and case reports (19-24). Accumulation of M3G in a dying patient due to a decline in renal function could therefore lead to undesirable adverse effects in this last phase of life. This neurotoxic effects of M3G seem to be enhanced by midazolam, a frequently used co-drug in the last phase of life (20).

Alternative opioids

Oxycodone, fentanyl, buprenorphine hydromorphone and methadone are commonly used alternative opioids for the treatment of pain. Only fentanyl and methadone don't have any known active renally cleared metabolites. It is recommended that only experienced physicians prescribe methadone, due to its high risk of cumulation as a result of its long and individually variable half-life. A risk of cumulation is also known for repeatedly parenteral administration of fentanyl, due to unpredictably increasing half-life, probably as a result of

reabsorption from other tissues because of its strong lipophilicity (25, 26). This makes both opioids less suitable as the opioid of first choice for CSCI.

Out of the remaining opioids oxycodone has the best characteristics to be used as the opioid of first choice for CSCI instead of morphine: the dosage for parenteral administration is the same as for morphine, in contrast to hydromorphone and buprenorphine (14). Costs are also barely different between parenteral oxycodone and morphine (27). Yet, in contrast to morphine, the central effects of circulating oxidative and reductive metabolites of oxycodone in humans are negligible (28). On theoretical considerations it is therefore hypothesized that oxycodone might be preferable over morphine for CSCI in terminal patients with a diminished renal function in order to reduce the risk of neurotoxic adverse effects. There is a striking lack of studies of sufficient quality investigating the clinical effect of this hypothesis. This lack of high quality evidence limits structural implementation in daily practice: the current relevant guidelines refrain from recommendations regarding oxycodone in renal impairment.

Delirium

Delirium is a common symptom in the last phase of life: it is estimated that up to 90% of patients in palliative care will develop a delirium at some point (29-31). Delirium is associated with high levels of distress for both patients, relatives and caregivers (32). As an ultimate consequence this could lead to the unwanted situation of a prematurely initiated palliative sedation, a process described as 'the destructive triangle' (33). The causes for delirium are multifactorial. Drugs in general are the main precipitating factor in the development of delirium in patients with advanced cancer (34). Opioids are considered to be one of the main groups of drugs that might play a contributing role in the development of delirium in patients with advanced cancer (35). A rational choice of opioids, aimed at reducing the risk of development of delirium, can therefore make an important contribution to the quality of this very last phase of life.

Recognition of pain and allodynia/hyperalgesia

Determining the presence of pain in dying patients could be complicated by reduced cognitive and communicative functions in the last days of life. 68-83% of the patients in this phase of life experience a decline in cognitive functions and 90-98% is not able to respond adequately anymore (36-40). It is probably even more difficult to recognize phenomena like allodynia (a pain response from a stimulus that does not normally provoke pain) or hyperalgesia () in this phase of life. It is therefore quite conceivable that in daily practice these symptoms are often misinterpreted as an increase in (nociceptive) pain. This could lead to dose escalation of the opioid in an attempt to control the assumed pain. In case of

morphine this dose escalation could subsequently result in aggravation of the painful sensation of allodynia/hyperalgesia due to further accumulation of M3G. Since allodynia and hyperalgesia are so difficult to recognize in the last days of life, there is much to be gained if the risk of occurrence of these two phenomena could be reduced by a rational choice of opioids.

Knowledge among Dutch physicians

Despite the negative recommendations in guidelines, widespread persistent prescription of morphine is still common practice nowadays: Masman et al. showed in 2015 that the vast majority (86,6%) of patients in a palliative care setting received morphine at the time of death (9).

Rurup et al. noted in 2010 that half of the Dutch physicians are not aware of increased plasma concentrations of morphine(-metabolites) in reduced renal functioning and that there was a demand for additional education on this subject among 83% of the physicians (41).

Because of the lack of studies of sufficient methodological quality that investigate possible differences in the neurotoxic adverse effects delirium and allodynia/hyperalgesia between CSCI with morphine and oxycodone for the treatment of pain in dying patients with diminished renal function, recommendations regarding preferences for a specific opioid can't be made at the moment. It is therefore not possible to fulfill this need for knowledge and training among physicians without further research.

2. OBJECTIVES

The objective of this study is to investigate whether and to what extent the occurrence of the neurotoxic adverse effects delirium and allodynia/hyperalgesia differs between morphine and oxycodone, administered by continuous subcutaneous infusion (CSCI), for the treatment of pain in dying patients with a diminished renal function.

Primary Objective

To compare the prevalence of delirium between oxycodone and morphine, administered by CSCI, for the treatment of pain in dying patients with a diminished renal function.

Secondary Objective

To compare the prevalence of allodynia/hyperalgesia between oxycodone and morphine, administered by CSCI, for the treatment of pain in dying patients with a diminished renal function.

Hypothesis

CSCI of oxycodone for treatment of pain in dying patients with a diminished renal function results in a reduced occurrence of the neurotoxic adverse effects delirium and allodynia/hyperalgesia in comparison to morphine.

3. STUDY DESIGN

This intervention study is designed as a randomized, controlled, observer blinded, multicenter, superiority trial (RCT) with two parallel groups with an 1:1-allocation-ratio. Patients with a diminished renal function, for this study defined as an eGFR of <50 ml/min/1.73m², who are eligible for continuous subcutaneous infusion (CSCI) of opioids for treatment of pain, are being randomized between morphine and oxycodone.

A double blinded study design is not feasible for budgetary reasons. This study is mainly funded by the ZonMw-program 'Palliantie – Meer dan zorg'. The costs involved in production, transportation and application of blinded study medication in accordance with all regulations, would result in exceeding the maximum budget allowed by this program. However, we think the probability of bias is low, as both treatment arms are active treatments, and none is clearly favored over the other with respect to analgesic properties and known side effects. Our hypothesis that oxycodone might be preferable over morphine to reduce the risk of delirium and/or allodynia/hyperalgesia is solely based on theoretical considerations. To date there is no clinical evidence of sufficient quality to accept or reject this hypothesis. It is therefore unlikely for a patient to present symptoms biased by the knowledge of his allocation to any particular study arm. In addition, the highly prevalent cognitive decline in the terminal phase of life makes it even more unlikely for a patient to be aware of – and thereby biased by – a possible theoretical difference in adverse effects of the assigned opioid.

When the treating physician expects that start of CSCI of an opioid for treatment of pain in a terminal patient could be a real short-term possibility, he or she will briefly explain the study to the patient and/or his or her legal representative and hand out the patient information sheet. An appointment with the researcher will be made for the same or the next day via a special phone number. The study will be explained verbally, either on site or by telephone, and any questions will be answered. After informed consent has been obtained from the patient or his/her legal representative randomization will be performed and CSCI with the corresponding opioid is initiated by the treating physician.

A delay in onset of treatment of pain should be avoided at any time. In case there is a need to start CSCI of an opioid immediately, participation is still possible if the participant or its legal representative is willing to provide written informed consent after explanation by the treating physician without an appointment with the researcher.

Outcome measures will be gathered by the research assistant 3 times a week until death of the participant. A venipuncture for the purpose of the determining the actual eGFR at baseline is performed at the first visit of the research assistant.

All deviations from the protocol will be documented.

Duration

The total time of follow-up is until death. The total duration of the study is 3 years.

Setting

Participating centers are nursing homes and hospices.

4. STUDY POPULATION

4.1 Population (base)

The study will be conducted in hospices and both somatic and psychogeriatric (PG) wards of nursing homes in Limburg, the southern part of the Netherlands. 15 nursing homes and 1 hospice are participating. The total number of beds in these locations is around 875 (350 somatic beds, 519 PG beds and 6 hospice beds), divided over 54 wards (24 somatic wards, 29 PG wards, 1 hospice). All of the participating locations are part of Envida, a health care organization in the region.

Both somatic and PG wards of nursing homes are included in this study, because CSCI with either morphine or oxycodone is already a common treatment in regular care for both patients with and without dementia (42-44). Inclusion of both patient groups would therefore best represent daily practice and optimizes applicability of the results. Special attention will be paid to the aspect of objection or resistance in the group of incapacitated patients, as further described in chapter 11.3.

Medical care in these nursing homes and hospices is provided by a permanent team of specialized physicians, employed by Envida. This allows for maximum adherence to the research protocol, because we are not dependent on varying external care providers, who might not be aware of the ongoing study, for the evening, night and weekend shifts.

Two other organizations, similar to Envida in size and population, intend to participate in this study at a later stage.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- minimal age of 18 years at the time of inclusion;
- the subject is in the terminal phase, i.e. death in the near future is expected by the treating physician;
- start of CSCI with an opioid for treatment of pain is indicated by the treating physician;
- willingness to allow one-time blood collection for assessment of renal function (eGFR);
- a signed informed consent is given by the participant or his/her legal representative.

4.3 Exclusion criteria

Anyone who meets any of the following criteria will be excluded from participation in this study:

- delirium at the time of inclusion;
- opioid induced hyperalgesia (OIH) at the time of inclusion;
- a medical necessity to apply a different opioid than morphine or oxycodone, such as previously demonstrated non-response to morphine or oxycodone (defined as a complete absence of any pain reduction after appropriate dosage), previously demonstrated unacceptable side effects of morphine or oxycodone, or a medical indication for an opioid with NMDA-receptor-antagonistic properties (currently only known for methadone);
- a documented allergy for morphine or oxycodone.

Subjects with an eGFR >50 ml/min/1.73m² should not be included in the study, because accumulation of metabolites is considered to be irrelevant in this range of renal functions. Despite this fact, we cannot formulate an unaffected renal function as an exclusion criterion prior to allocation, because the time needed for assessment of the renal function could lead to either an unethical delay in treatment of pain or occurrence of death even before the lab results are known. Therefore renal function is assessed after inclusion. In case a subject turns out to exceed the threshold of 50 ml/min/1.73m², this will be considered as meeting an extended exclusion criterion and the subject concerned will be replaced by a new subject.

4.4 Sample size calculation

Sample size calculation is performed for the primary objective, i.e. the comparison of the percentage of patients who develop delirium in the period between start of CSCI with oxycodone (intervention group) or morphine (control group) and death. Although we expect the intervention group to perform superior to the control group in this respect, this hypothesis is purely based on theoretical considerations. No former (clinical) studies of sufficient quality exist to rule out the possibility that the intervention group actually turns out to perform inferior to the control group. Therefore sample size calculation is based on a two-tailed test. Based on the available literature, the percentage of delirium in terminal patients is estimated at 86% (29, 30, 45). A difference of 15% is considered to be clinically relevant. The probability of a type 1 error is fixed at 5%. Groups are analyzed according to

the intention to treat principle. In order to achieve a power of 80% for detecting a clinically relevant difference, 117 patients per group are needed.

In order to assess feasibility, we counted the number of terminal patients with CSCI of opioids in the daily medical reports for evening-, night- and weekend shifts of physicians of Envida for 3 months in 2016. Extrapolation of these results lead to a number of 120-150 terminal patients with CSCI of opioids within Envida in 1 year. In addition, we searched the electronic medication prescription system of Envida for prescriptions of CSCI of opioids in deceased patients for 5 months in 2017. This search resulted in 52 patients with CSCI of an opioid for this period, which can be extrapolated to 125 patients per year.

Both of these two separate observations resulted in approximately 120 patients with CSCI of an opioid per year per organization. For the intended 2-year inclusion period within 3 (comparable) organizations, this would result in an estimated total of 720 eligible patients. In order to achieve the required number of participants 32,5% of the eligible patients should be willing to participate in our study. This study was presented to the members of the central client council of Envida, who are representative for the intended study population. The expectation of this council was that the willingness to participate would be high.

An exact estimation of the number of subjects that have to be replaced after inclusion due to an eGFR $>50 \text{ ml/min/1,73m}^2$ is not possible, because these data do not exist for our study population. A recent study showed that about half of the study's participants developed an eGFR $<60 \text{ ml/min/1,73m}^2$ by the time they reached the terminal phase of life (46). Based on this study's findings we make a rough estimate that 117 would meet the extended exclusion criterion of an eGFR $<50 \text{ ml/min/1,73m}^2$. However, compared to our study population of mainly frail elderly, the population in this study was younger, had less comorbidity and had a lower percentage of subjects that had pre-existing kidney disease (14% vs. 26%). Combined with the clinical experience of elderly care physicians of a rapid decline in renal function during episodes of intercurrent illness in this frail population, it is thought to be safe to assume that the number of eligible subjects provides sufficient reserve to replace participants with an eGFR $>50 \text{ ml/min/1,73m}^2$. Despite this clinical experiences that would indicate a lower number of included subjects, we have to make a larger estimate of **a total of 351 included participants**, based on the limited available evidence.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The investigational products are oxycodone and morphine. After inclusion a participant will start with continuous subcutaneous infusion (CSCI) of either oxycodone or morphine as determined by randomization. Both continuous administration by a syringe driver as well as bolus administration every 4 hours will be regarded as CSCI.

5.2 Use of co-intervention

In both groups all pharmacological and non-pharmacological co-interventions for treatment of any occurring symptoms are allowed. All participating physicians are advised to apply these co-interventions in accordance with the 'Palliative-guidelines', i.e. the Dutch palliative guidelines, provided by the IKNL (47). All pharmacological co-interventions will be registered.

Palliative sedation as a co-intervention is allowed when all requirements of the guideline 'Palliatieve sedatie' of the KNMG are met (48).

5.3 Escape medication

Escape medication for breakthrough pain can be applied in accordance with the Dutch 2016 guideline 'diagnostiek en behandeling van pijn bij patiënten met kanker' (14):

- a Rapid-Onset Opioid (ROO), i.e. transmucosal or intranasal administered formulations of fentanyl; *or*:
- a subcutaneous bolus injection of the same opioid as administered by CSCI in a dosage of 10-15% of the 24-hour CSCI-dosage, up to a maximum amount of 6 boluses per 24 hour.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Oxycodone Hydrochloride Solution for Injection or Infusion:

An opioid agonist, regular on the market in the Netherlands and known in Dutch as 'oxycodon injectievloeistof' or 'OxyNorm® injectievloeistof'.

Morphine Hydrochloride Solution for Injection or Infusion:

An opioid agonist, regular on the market in the Netherlands and known in Dutch as 'morphine injectievloeistof'.

6.2 Summary of findings from non-clinical studies

We refer to the Summary of Product Characteristics (SPC) of both products.

6.3 Summary of findings from clinical studies

In a recent systematic review regarding the use of opioids in cancer patients with renal impairment only 15 studies were identified: 8 prospective observational and 7 retrospective studies, all of which were judged of low quality. Morphine was by far the most investigated opioid. Indications that morphine metabolites play a role in causing adverse effects in renal impairment were inconsistent (49).

A more recent cross-sectional multicentre study comparing the side effects of morphine, fentanyl and oxycodone in 1147 cancer patients found that patients with higher M3G serum concentrations were more likely to have severe cognitive dysfunction than patients with lower M3G serum concentrations (OR: 1.63; 95% CI: 1.03-2.56; p=0.04), whereas patients with higher oxycodone serum concentrations were only more likely to report severe fatigue (OR: 1.70; 95% CI: 1.04-2.78; p=0.03) than patients with lower oxycodone serum concentrations. It didn't show any association between renal function and differences between opioids in cognitive functioning or pain. However, the applied measuring instrument (EORTC QLQ-C30) does not determine presence of delirium or allodynia/hyperalgesia (50).

6.4 Summary of known and potential risks and benefits

Both morphine and oxycodone are strong opioids with well-documented analgesic abilities. Both share the side effect profile of strong opioids: constipation, sedation, nausea, vomiting, dizziness, hypotension. Both investigation products in this study are used within the registered indications.

6.5 Description and justification of route of administration and dosage

The two investigated products, morphine and oxycodone, are both registered products for continuous subcutaneous infusion, as described in the 'KNMP Kennisbank' as well as in the IKNL-guideline 'Pain' (51-53). Widespread use of both of these opioids as well as the continuous subcutaneous route of administration are an essential part of common practice in treatment of pain in terminally ill patients.

6.6 Dosages, dosage modifications and method of administration

All participating physicians are asked to perform dosage and dosage modifications in accordance with the Dutch 2016 guideline 'diagnostiek en behandeling van pijn bij patiënten met kanker' (14). The medication lists collected by the research assisted in sealed envelopes at each visit, are analysed by the researcher for indications of deviations from this directive on dosage. In case a deviation is suspected, it will be recorded and further investigated by the researcher.

6.7 Preparation and labelling of Investigational Medicinal Product

After randomization the treating physician will initiate CSCI with the assigned opioid by following the regular local procedures and protocols, applicable to the institution where he or she is employed, for prescription, distribution and administration of medication.

6.8 Drug accountability

The regular local procedures and protocols of the individual institutions, all of which comply with the Dutch Opium Act, apply.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

The objective of this study is to determine whether there are any relevant differences in the occurrence of the neurotoxic side effects delirium and allodynia/hyperalgesia between the intervention group receiving oxycodone and the control group receiving morphine. All parameters will be assessed three times a week by a trained research assistant, who will be blinded for the assigned opioid until death of the participant.

8.1.1 Main study parameter/endpoint

The occurrence of the neurotoxic adverse effect delirium at any time between start of CSCI with the opioid and death.

The Delirium Observation Screening (DOS)-scale is scored by the nursing staff on a daily basis and collected 3 times a week by the research assistant to screen for presence of delirium (54). In case this screening instrument indicates a possible presence of delirium, the researcher will ask the treating physician to confirm or reject the clinical diagnosis of delirium in accordance with the DSM-IV-TR criteria (55).

8.1.2 Secondary study parameters/endpoints

The occurrence of the neurotoxic adverse effect allodynia/hyperalgesia at any time between start of CSCI with the opioid and death.

Presence of allodynia or hyperalgesia is assessed by a trained research assistant by asking the subject whether respectively lightly brushing with a piece of cotton wool on the skin or performing pin-prick testing provokes pain or aggravates already existing pain (56, 57). In case the subject is not able to adequately respond verbally the items of the Rotterdam Elderly Pain Observation Scale (REPOS) are used to determine presence of a painful response (58, 59).

8.1.3 Other study parameters

The following baseline characteristics will be recorded at the time of a participant's inclusion:

- Age
- Gender
- Stay in hospice or at somatic or psychogeriatric nursing home ward
- Medication use prior to start of CSCI
- Creatinine (by one time blood collection) and calculated eGFR (by use of the CKD-EPI-formula)
- Main diagnosis and co-morbidities

The following other data will be recorded:

- time between start of CSCI with oxycodone or morphine and death
- pain scores (NRS or REPOS) prior to testing at each visit of the research assistant
- current medication use at each visit of the research assistant
- reported side effects as observed by the nursing staff
- quality of death, perceived by relatives.

A detailed description of the procedures used to determine the study parameters is provided in chapter 8.3.

8.2 Randomisation, blinding and treatment allocation

Randomization is performed by the web based randomization program ALEA, hosted by the CTCM. In order to prevent an uneven distribution of relevant prognostic factors, allocation will be stratified by means of minimisation for type of ward (somatic or psychogeriatric, representing absence or presence of a clinical relevant stage of dementia and thereby indirectly also status of mental and communicative capabilities), for presence or absence of opioid use at baseline and age. It is not possible to perform stratification for the level of renal impairment, since it is not possible to determine the renal function prior to randomisation (for afore mentioned reasons). In case this might result in any imbalance between the study arms, the differences will be compensated for in statistical analysis.

When a patient is eligible for inclusion the treating physician will contact the research-team by telephone. After verification of the in- and exclusion criteria and signing informed

consent, the researcher will perform randomization by accessing ALEA. The treating physician is subsequently informed of the opioid assigned by this randomization procedure. The phone number for randomization is available 24/7 in order to prevent any delay in onset of treatment of pain.

The trained research assistant, who will measure the participant's outcome parameters on location, will only be provided with personal and location data needed to visit and identify the participant by the researcher. The research assistant does not receive any information regarding the assigned opioid.

8.3 Study procedures

After inclusion and allocation to either morphine or oxycodone participants will be visited by the research assistant three times a week until death. During this period of follow up all participants will undergo the following procedures to determine the predefined research parameters (see also figure 1 for a flow-chart of the study procedures and table 1 for a description of the individual procedures):

At the first visit after inclusion a one-time venipuncture will be performed to collect blood to determine the creatinine level in laboratory testing performed by the Central Diagnostic Laboratory of the Maastricht University Medical Centre. This result is used to calculate the eGFR at baseline by using the CKD-EPI-formula. In case a participant has no diminished renal functioning, defined as an eGFR <50 ml/min/1.73m², he or she will be withdrawn from the study and consequently excluded from data collection. These withdrawn subjects will be replaced by new subjects in order to achieve the required sample size.

All other procedures will be performed at each visit of the research assistant.

Two weeks after a participant's death, and only when a participant or his legal representative has given permission in the written informed consent, a significant other or legal representative will be contacted by telephone by the researcher to ask whether he or she is willing to participate in an interview in which the perceived quality of dying is assessed by using the Quality of Dying and Death (QoDD) Questionnaire.

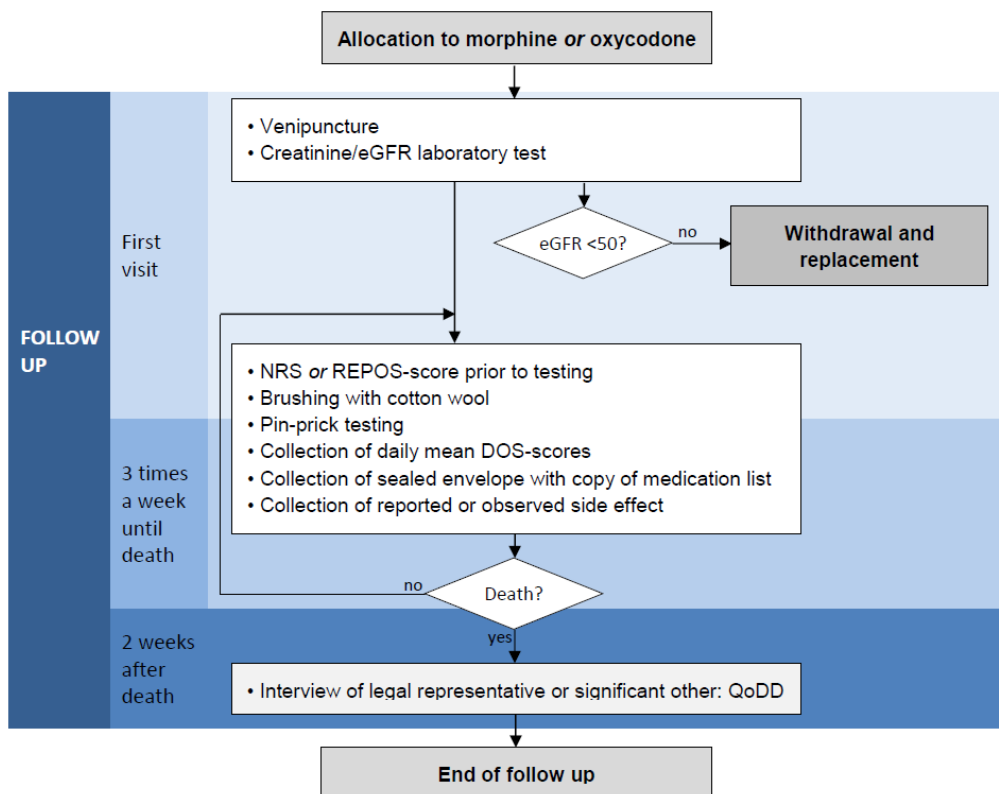


Figure 1: Flow chart of study procedures

Depending on the ability of the subject to adequately respond verbally either the 0-10 Numeric Rating Scale (NRS) or the Rotterdam Elderly Pain Observation Scale (REPOS) will be used to assess pain prior to testing. Subsequently the NRS or REPOS will be scored again while performing brushing with cotton wool and pin-prick testing to assess for presence of allodynia and hyperalgesia respectively.

Delirium Observation Screening (DOS)-scores, assessed by the nursing staff three times a day, are collected by the research assistant and analysed by the researcher. In case the mean daily DOS-score exceeds the cut-off point of 3 points, the suspected diagnosis of delirium needs to be confirmed or rejected by a clinician. The DOS is an easy to use nurse-based observation instrument without the need for prior training. Despite the nursing staff not being blinded for the assigned opioid, the risk of missing delirious subjects during this screening is negligible, because of its negative predictive value close to 100% (60-62). In order to perform a blinded confirmation or rejection of the final diagnosis after this screening, this procedure will be performed by a psychologist, who is not aware of subjects' medication use. Availability of a psychologist on each ward is part of the regular care in Dutch nursing home settings.

The research assistant will also collect sealed envelopes with a copy or print of the medication list of each participant at each visit. These envelopes are sealed to guarantee blinding of the research assistant. The collected medication lists are assessed by the researcher for:

- use of co-medication for treatment of delirium;
- use of co-medication for treatment of allodynia/hyperalgesia;
- use of sedatives for palliative sedation;
- use of co-medication that might provoke delirium;
- adherence to the protocol for opioid dosage.

Table 1: Description of study procedures

	Procedure	Parameter	Description
Invasive procedures	Venipuncture	eGFR ¹⁾	One-time blood collection for laboratory assessment of the renal function (eGFR) at the first visit of the research assistant, who is qualified and competent to perform this procedure. Blood samples will be transported to the laboratory in a transportation box meeting UN3373/P650-specification in accordance to the ADR regulations.
	Creatinine	eGFR ¹⁾	This laboratory test is performed from the collected blood sample by the Central Diagnostic Laboratory of the Maastricht University Medical Centre in order to calculate the eGFR at baseline by using the CKD-EPI-formula (63).
Physical examination	Touching and lightly brushing with a piece of cotton wool	Allodynia ²⁾	This procedure is performed 3 times a week on both arms and legs by the research assistant. A painful sensation or an increase in pain as a result of the procedure is indicative for the presence of allodynia (56, 57).
	Pin-prick testing	Hyper-algesia ³⁾	This test is performed 3 times a week by the research assistant. A standardized method is used by putting a free floating 23G needle in a 2 ml syringe with the plunger removed perpendicular to the skin. This procedure is performed on both arms and legs. A painful sensation or an increase in pain as a result of the procedure is indicative for the presence of hyperalgesia (56, 57).

Table continues on the next page

Questionnaires	Delirium Observation Screening (DOS)	Delirium	This observational screening instrument for delirium is completed on a daily basis by the nursing staff. The results are collected three times a week by the research assistant. In case a DOS-score exceeds the cut-off point of 3 points a notification will be send by the researcher to the ward's psychologist and he or she will be asked to confirm or reject the clinical diagnosis of delirium (54).
	0-10 Numeric Rating Scale (NRS)	Pain prior to testing	The NRS is used to quantify the level of pain experienced by a subject who is able to respond verbally (64).
	Rotterdam Elderly Pain Observation Scale (REPOS)	Pain prior to testing, allodynia ²⁾ and hyperalgesia ³⁾	In case a participant is no longer able to adequately verbally report presence or absence of pain the items of this observatory instrument are used by the research assistant to determine the presence of pain prior to testing and to objectify the physical reactions to the brushing with a piece of cotton wool and the pin-prick test, which will evoke a sensation of pain when allodynia/hyperalgesia is present. The REPOS, originally designed to detect pain in non-communicative and cognitively impaired nursing home residents, has recently also been validated for detection of pain in non-communicative terminal patients (58, 59).
	Quality of Dying and Death (QoDD)	Quality of dying, as percveived by relatives	Quality of dying, as perceived by relatives, is assessed by the researcher two weeks after a participant's death in an interview. This interview only takes place when both written informed consent is given by the participant, and the relative is willing to participate (65).

¹⁾, ²⁾, ³⁾: procedures with corresponding numbers are used in conjunction for determination of the mentioned parameter

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time if they wish to do so, without the need to provide any reason and without any consequences.

8.4.1 Specific criteria for withdrawal

A subject will be withdrawn by the researcher in case the eGFR at baseline, as determined from the blood collected by venipuncture at the first visit after randomization, turns out to be $>50 \text{ ml/min/1.73m}^2$. This is considered as an extended exclusion criterion.

Participants will be withdrawn by the researcher or the treating physician in case of any of the following conditions:

- the condition of the participant has changed in such a way that there is no longer a medical indication for administration of opioids;
- the assigned opioid leads to side effects that are perceived as unacceptable by the individual participant (for example persistent nausea, pruritus or drowsiness);
- there is a medical need to rotate to a different opioid than assigned;
- continuation of CSCI is impossible due to patient related, situational, mechanical or practical reasons or circumstances;
- a participant is transferred to a non-participating institution.

8.5 Replacement of individual subjects after withdrawal

Only in case of withdrawal as a result of meeting the extended exclusion criterion, i.e. an $\text{eGFR} > 50 \text{ ml/min/m}^2$, participants will be replaced. In all other cases participants will not be replaced after withdrawal from the study, in accordance with the intention-to-treat principle.

8.6 Follow-up of subjects withdrawn from treatment

In case a participant wants or needs to be withdrawn from the study treatment, he or she will be asked for permission for continuation of follow-up to allow full intention-to-treat analysis.

8.7 Premature termination of the study

The study will immediately be terminated prematurely when interim analysis shows signs of serious disadvantage for the participants in one of the groups in comparison to the other group. In case this situation occurs, the researcher will ensure that the METC, all participants and all participating institutions are informed. From that moment on the treating physician of each individual participant will determine which opioid is most suitable for continuation of the treatment of pain according to existing guidelines.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to administration of morphine or oxycodone. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. Known side effects, as registered in 'Kennisbank KNMP', are not considered as AEs.

9.2.2 Serious adverse events (SAEs)

A serious adverse event (SAE) is any untoward medical occurrence or effect that:

- results in death within 120 minutes after start or increase of dosage of CSCI of morphine or oxycodone (explained in more detail below); *or*
- requires hospitalisation; *or*
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

Death as a SAE in terminally ill patients

Since participants are terminally ill patients, death is an inevitable event as a result of the ongoing dying process caused by the underlying terminal disease. The end point of follow-up is defined as the moment of death. So death is to be expected for every subject. The vast majority of deaths are therefore not to be regarded as SAEs.

Available evidence focusing on the relationship between administration of opioids and death in the study population, i.e. terminally ill patients with pain, suggest that it is unlikely that death of a subject in this very specific population is related to the administration of an opioid: although opioids can cause respiratory depression in healthy volunteers without pain, multiple studies have shown that clinically relevant respiratory depression does not occur when opioids are titrated against pain (66-70). Considering assumed concerns about potential life-shortening effects of opioids from a broader perspective than only by means of respiratory depression, studies focusing on survival in relation to opioid use and dosage not only confirm that survival is not affected negatively when titrated against symptoms, but even suggest a possible association with an prolonged life-expectancy, especially at higher dosages (3, 71-75).

Although theoretically unlikely, as explained in the previous section, we consider the possibility of a contribution of the investigated product to occurrence of death when a time-dependent relationship exists between death and administration of the product.

Available pharmacokinetic data in this respect are limited to:

- T_{max} of rectally administered morphine: 45-60 minutes (52);
- T_{max} of orally administered oxycodone: 90 minutes (53);
- time to maximal analgesia of subcutaneous administered morphine: 50-90 minutes (52).

A causal relationship between administration of morphine or oxycodone and death is more plausible when death occurs within the timeframe of reaching C_{max} and/or maximum therapeutic effect. Based on the pharmacokinetic data mentioned above, with some margin added, death is only considered as a SAE when it occurs within the first 120 minutes after start or increase of dosage of CSCI of the opioid.

Handling of SAEs

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal '*ToetsingOnline*' to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a

period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the Summary of Product Characteristics (SPC) for an authorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal '*ToetsingOnline*' to the METC :

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal '*Eudravigilance*' or '*ToetsingOnline*' is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will

be maximal 7 days for a preliminary report with another 8 days for completion of the report.

Breaking the code for SUSAR reporting

The study design is observer blinded. The randomly assigned opioid is prescribed by the treating physician and supplied according to local procedures. Medical care is provided by a permanent team of physicians with uniform medical records. In case of a medical emergency the treating medical team is therefore always aware of the assigned opioid and the research assistant does not need to be unblinded.

Consequently a specific procedure for breaking the code in case of an emergency is not necessary.

For SUSAR reporting the following procedure has to be followed:

1. A copy of the medication list or a printout of the electronic medication prescription system is made by the treating physician.
2. This copy or printout is placed inside a non-transparent envelope.
3. The envelope is sealed and a signature is put over the envelope flap to ensure that the seal can't be broken unnoticed.
4. The date, time and location of sealing are noted on the envelope, as well as the name of the person performing the sealing.
5. The sealed envelope is collected by the research assistant, CI or PI.
6. Only the CI and PI are allowed to break the seal and open the envelope. Before opening the envelope they should ensure themselves that no other, unauthorized persons can see the contents.
7. The CI/PI opening the envelope keeps a code breaking log, that registers:
 - a. patient trial number;
 - b. reason for breaking the code (in this case: SUSAR reporting);
 - c. name of the person requesting the code break;
 - d. date, time and location of sealing the envelope, as noted on the envelope;
 - e. name of the person sealing the envelope, as noted on the envelope;
 - f. date, time and location of breaking the seal and opening the envelope;
 - g. name of the CI/PI breaking the seal and opening the envelope;
 - h. signature of the CI/PI breaking the seal and opening the envelope.

By using the participant's actual medication list instead of only the randomization outcome the CI/PI can also check for prescription or dosing errors of the assigned opioid in SUSAR reporting.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable.

10. STATISTICAL ANALYSIS

A table with baseline characteristics will be provided for both groups. We will assess these baseline characteristics for any imbalance between both study arms. In case any imbalance exists, we will consider whether this is a potentially clinically relevant confounder. When considered clinically relevant, we will correct for this imbalance in statistical analysis. Randomization is stratified for what we consider to be the main potentially clinically relevant confounders, i.e. 'stay on a psychogeriatric ward', 'former use of opioids' and age. We do therefore not expect any imbalance in this regard. However, since renal function can only be assessed after allocation, stratification can't be performed for stage of renal impairment, i.e. moderate (eGFR 30-50 ml/min/1.73m²), severe (eGFR 15-29 ml/min/1.73m²) or endstage (eGFR <15 ml/min/1.73m²). It is therefore not unlikely that any imbalance could arise in the distribution of the various stages of renal impairment. As the degree of accumulation of metabolites is related to the degree of renal impairment, we consider this imbalance to be the most important confounder that needs to be corrected for.

All analyses will be performed according to the intention-to-treat principle. The risk of a degree of cross-over after allocation to the extent that it might affect outcome parameters, is considered low for the same reasons that it is thought to be unlikely for subjects to be biased by the knowledge of the assigned opioid, as explained in the study design (chapter 3), i.e. no known difference in side effects between the two opioids and a highly prevalent cognitive decline in the terminal phase of life. In addition, in daily practice switching of opioids barely occurs in this phase of life due to the limited time between start of CSCI with an opioid and death.

Imputation techniques will be used for supplementation of incomplete data, thereby guarantying analysis of all participants in the group they were assigned to by randomization. The method we will use will depend on the proportion of missing values and on the assumptions that can be made about the missingness mechanism after collection of the data: In case the percentage of incomplete cases is less than, or equal to, 5%, we will use single stochastic imputation to impute the dataset, as the difference in precision due to not taking between-imputation variance into account is likely to be negligible. If the proportion of incomplete records exceeds 5%, multiple imputation will be used. In that case, the number of imputations will be set to 10. For both imputation strategies, the imputed values will be drawn using predictive mean matching with a fully conditionally specified model. If, after collection of the data, we expect that data are missing not at random, we will impute using a missing not at random mechanism (again,

using single or multiple imputation), and perform a sensitivity analysis to see whether our conclusions are robust.

10.1 Primary study parameter(s)

Pearson's Chi-squared test will be used to assess whether there is any distinction between both groups in the proportion of patients in whom delirium has occurred. In case the analysis of the baseline characteristics showed any clinically relevant imbalance, we will also perform a multivariable logistic regression analysis in order to correct for this imbalance.

10.2 Secondary study parameter(s)

Depending on the level of measurement a Chi-squared test or a T-test will be used to assess differences in secondary study parameters, and logistic and linear regression for baseline-corrected estimates.

10.3 Interim analysis

An interim analysis is performed at a predefined clinically relevant moment in order to determine whether continuation of the study is considered safe for the study's participants. The moment of interim analysis and the criterion for safety have been determined by means of clinical expert consensus.

This interim analysis will be performed for the primary and secondary study parameters after the end of follow up, i.e. death, of the first 30 participants in each group.

A difference between the intervention and control group of more than 50% for the primary study parameter is considered to be an indication that one of the groups is significantly harmed more than the other. When this difference can't be contributed to other factors, like an uneven distribution of baseline characteristics, especially other medication use, it is considered unethical to withhold one of the groups from the superiority of one of the opioids. Therefore, this potential situation is regarded as a stopping rule.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the 7th Declaration of Helsinki (Fortaleza 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

All patients and/or their legal representatives of participating wards will receive an information leaflet, briefly explaining that their ward is participating in the study and that they can be asked for their willingness to participate by the time they'll meet the inclusion criteria.

When the treating physician of a patient on a participating ward expects that start of CSCI of an opioid for the treatment of pain in a dying patient could become a real short-term possibility, he or she will briefly explain the study to the patient and/or his/her legal representative and hand out the patient information sheet, which explains the objectives and methods of the study in understandable language. The treating physician informs the researcher via a special telephone number. The researcher will make an appointment with the patient and/or his/her legal representative for the same or the next working day. The study will be explained verbally, either on site or by telephone, and questions will be answered. Also the opportunity to consult an independent physician is emphasized.

Subjects will only be included in the study after written informed consent is obtained by the treating physician.

This study should never lead to a disturbance of usual care. Especially a delay in onset of treatment of pain should be avoided at any time. Usually start of CSCI of an opioid is part of advance care planning, resulting in enough time for the researcher to contact the patient or its legal representative and thereafter for the subjects to consider participation. However, since medical conditions in dying patients could become unstable unexpectedly, resulting in a rapid deterioration and need to start CSCI of an opioid sooner than initially expected, available time for explanation by the researcher and subsequent consideration by the subject is variable. In case there is a need to start CSCI of an opioid immediately, participation is still possible if the participant or its legal

representative is willing to provide written informed consent after explanation by the treating physician without an appointment with the researcher.

11.3 Objection by incapacitated subjects

Since the major part of dying patients experiences a decline in cognitive functions and are not able to respond adequately anymore, it is essential to include this incapacitated population in our study (36-40). When a participant is or has become incapacitated as a result of his medical condition or cognitive impairment, his or her legal representative decides whether the subject will be participating in the study or not, unless the subject previously has stated explicitly otherwise. The Dutch law WGBO determines which persons are entitled to act as legal representatives. Signs of consistent objection or resistance to any of the study procedures after inclusion, especially the invasive procedure (venipuncture), have to be considered as an expression of the participant's wish to not participate in the study any longer. Consequently he or she will be withdrawn from the study immediately. In case a incapacitated participant shows signs of objection or resistance to the continuous subcutaneous route of administration (for example by removal of the infusion tube or needle) the treating physician will decide whether continuation of CSCI of an opioid is a medical necessity to avoid severe suffering from pain. When there is no medical necessity or when adequate pain control can be achieved otherwise, it is not allowed for the subject to participate in the study any longer and he/she will be withdrawn from the study according to the criterion 'continuation of CSCI is impossible due to patient related, situational, mechanical or practical reasons or circumstances' as described in section 8.4.1.

11.4 Benefits and risks assessment, group relatedness

Participants assigned to the oxycodone group could potentially benefit from the theoretically hypothesized reduced risk of developing delirium and/or allodynia/hyperalgesia compared to the morphine group. This potential benefit for the oxycodone group is to be regarded with a considerable amount of uncertainty, since no former evidence of sufficient quality exist to accept or reject this hypothesis. Furthermore, both CSCI with oxycodone and morphine are already established treatments for pain in palliative care and part of common medical care in the Netherlands. The choice for either one of these opioids is seldom based on patient characteristics, but more likely to be determined by personal preferences or experiences of individual

physicians or institutions. Therefore potential drug-related benefits or risk, if any would exist, do not differ from care as usual.

Potential disadvantages of participation in this study in general could be:

- possibly experiencing some transient inconvenience from study procedures, such as the one-time venipuncture and cotton wool/pin prick test;
- visits of an unfamiliar person 3 times a week during the last phase of life;
- loss of time of approximately 5 to 10 minutes per visit;
- a participant must adhere to the study protocol.

The risk of venipuncture-related complications is considered low, as further explained in chapter 13.2.

11.5 Compensation for injury

Envida has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor also has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides coverage for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Not applicable: participants nor participating institutions will receive any kind of remuneration or compensation for participation in the study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All data in this study will be handled digitally by use of electronic Case Report Forms (eCRF) and the data management system MACRO, both provided and hosted by the Clinical Trial Center Maastricht (CTCM). These systems comply with all applicable regulations regarding data security. Only authorized personnel will have access to these systems. Data storage is secured by the CTCM by regular back-ups. Data will be stored for 15 years.

No identifiable reference to subjects will be made in analysis, reports or publications. To protect the confidentiality of subjects all data will only be linked to a subject by a numeric identification code, of which the key will be safeguarded by the investigator.

Blood samples for determining the eGFR to decide whether the extended exclusion criterion is met, are processed by the Central Diagnostic Laboratory of the Maastricht University Medical Centre. This laboratory needs the samples to be identifiable. The laboratory results will be delivered by SAP, the electronic patient file system of the Maastricht University Medical Centre. These results will be entered into the eCRF by the researcher and will be linked to a subject by code only from thereon. Blood samples will be destroyed by the laboratory after 1 week and will not be used for any other purpose than described in this study protocol.

Publication

Public disclosure and publication of the research data will be according to the CCMO statement on publication policy

12.2 Monitoring and Quality Assurance

This study will be registered at clinicaltrials.gov. Monitoring will be performed by the Clinical Trial Center Maastricht (CTCM), an independent institution which follows the international ICH-GCP (Good Clinical Practice) guidelines.

The monitoring plan will at least consist of the following aspects: and at least incorporate the following items:

- Verification of the informed consents, inclusion and exclusion criteria, reported SAEs and SUSARS, and Case Report Forms (CRFs).

- Site Initiation Visit (SIV): during the SIV the Trial Master File/Investigator Site File (TMF) will be verified. In addition, all aspects of the protocol will be checked, including personnel responsibilities.
- Interim Monitoring Visit (IMV): during the IMV all documentation will be checked and CRFs are being verified according to the source documents.
- Close-Out Visit (COV): during the COV a final verification of the TMF will be performed and all outstanding issues will be finalized.

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

Public disclosure and publication of the research data will be performed in accordance to the CCMO statement on publication policy.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

Since the investigated products are registered products to be used in regular care for the registered indication and route of administration, and not in combination with other products, and the risk of venipuncture-related complications is considered low, as further explained in chapter 13.2, this chapter is not applicable.

13.2 Synthesis

Investigational products

The two investigated products, morphine and oxycodone, are both registered products for CSCI, as described in the 'KNMP Kennisbank' as well as in the IKNL-guideline 'Pain'. Widespread use of both of these opioids as well as the continuous subcutaneous route of administration are an essential part of common practice in treatment of pain in terminally ill patients. Since the indication, dosage and use of the products in the study does not differ from the registered use in common practice, participants are not exposed to any additional medication-related risks.

Venipuncture

A one-time blood collection by venipuncture is not a common procedure in regular care for terminal patients receiving CSCI with morphine or oxycodone for treatment of pain. It could therefore pose a potential additional risk to participants.

Potential risks associated with venepuncture are hematoma formation, infection, nerve damage, syncope or fainting or excessive bleeding. However, the risk of venipuncture-related complication is considered very low: a recent study, analysing 1.082.053 venipunctures in 10 years, showed an incidence rate of 0,0271% for any venipuncture-related complication and 0,0015% for obvious nerve injuries. No patients exhibited persistent severe symptoms (76). These findings are in line with an similar older study (77). Higher incidence rates of nerve injuries have been reported for blood donation-related venipunctures. The incidence rates range from 0,0144% to 0,0158% and therefore still imply a low risk (78, 79).

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